DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

March 16, 2006

The Honorable Mark E. Souder
Chairman
Subcommittee on Criminal Justice,
Drug Policy and Human Resources
House Committee on Government Reform
Washington, D. C. 20515-6148

Dear Mr. Chairman:

Thank you for the letter of December 21, 2005, in which you request that the Food and Drug Administration (FDA or the Agency) provide information and respond to several questions concerning Mifeprex® (mifepristone, also known as RU-486).

Consistent with the agreement reached after discussions between your staff and me, we are unable to send some of the detailed personal medical information you requested. At this time we are able to provide a copy of one autopsy report that already has been made available in the public domain. We are in the process of determining the public availability of the three other autopsy reports you requested and we will provide them to you if we determine they are in the public domain. We are enclosing a number of public documents concerning the events leading up to and including the approval process for Mifeprex.

In response to your specific questions, we can tell you that FDA did investigate thoroughly the August 2001 death of the Canadian woman who previously had taken RU-486 during a clinical trial. The Agency also reviewed the limited information available for the British death in May-June 2002 and determined it was not caused by septic shock, but rather by a perforated stomach ulcer as reported by the United Kingdom on June 18, 2002.

FDA has investigated, to the extent practicable based on the information available to the Agency, all deaths reported to the Agency associated with the use of mifepristone and misoprostol and has confirmed that the four cases identified in your letter of fatal infection (sepsis) that occurred in the United States tested positive for *Clostridium sordellii*. In addition to the reported deaths of these four California women who had taken Mifeprex, as of November 5, 2005, FDA is aware of 12 post-marketing reports of other patients who became septic after undergoing a medical abortion. These severe cases of infection did not result in death.

The Agency continually evaluates and monitors the frequency and risk of all serious and/or life-threatening adverse events for all approved drugs including mifepristone. With respect to your inquiry regarding non-sepsis related deaths, to date, the reported events do not appear to indicate an overall safety risk for this product that is greater than the expected risk. FDA usually does not review state records to monitor for adverse events of drug products, and FDA did not do so here. FDA has not examined Medicaid payment records from any states to look for admissions for infections that may be associated with use of mifepristone and misoprostol but were not reported directly to the Agency.

The FDA approved regimen for medical abortion consists of taking 600 milligrams (mg) (three 200 mg tablets) of oral Mifeprex on Day 1 and 400 mcg (two 200 mcg tablets) of oral misoprostol on Day 3. FDA is aware that many medical practitioners use modified regimens, which may include prescribing different doses of Mifeprex and misoprostol, dosing misoprostol on a different day, and/or advising patients that the oral misoprostol tablets may be inserted into the vagina. While some of the modified regimens have been well described in the medical literature, the safety and effectiveness of Mifeprex and misoprostol dosing regimens other than the one approved by FDA, including use of oral misoprostol tablets intravaginally, has not been established by FDA. Because we do not know enough about the risk factors for *Clostridium sordellii* infections, which are rare, we cannot speculate about *Clostridium sordellii* infection in other obstetrical and gynecologic settings.

With regard to the November 2004 labeling change you mention, FDA worked as expeditiously as possible in order to inform the public of the risk of bacterial infection reported in patients after use of mifepristone. The labeling change was approved on November 15, 2004, just 3 months after the third death was reported to FDA on August 10, 2004.

Your letter questions whether the serious and life-threatening bleeding cases reported after use of the Mifeprex regimen could have been caused by *Clostridium sordellii.* Findings of hemorrhage and infection are seen with all types of abortion, pregnancy, and childbirth. The hemorrhage associated with *Clostridium sordellii* infection is internal and the constellation of clinical findings for sepsis associated with it is highly unusual. Therefore, the possibility that *Clostridium sordellii* infection caused some of the reported serious cases of external bleeding that were not accompanied by the associated signs of serious sepsis is very unlikely.

Because cases and medical experience with *Clostridium sordellii* infections are very rare (approximately 1 in 100,000), the knowledge and expertise about this organism is limited to a few individuals. The basic science and epidemiology of *Clostridium sordellii* colonization, activation of toxin production, and the effects, if any, of drugs and other factors on *Clostridium sordellii* in women who are in their first trimester, are not well understood.

In an effort to further explore the science in this area, FDA is working collaboratively with The Centers for Disease Control and Prevention and the National Institute of Allergy and Infectious Diseases to better understand this infection both in general and in the context of medical abortion. To this end, FDA announced in the February 14, 2006, *Federal Register* (FR) at pages 7778-9 (copy enclosed) a Public Workshop on Emerging *Clostridial* Disease to be held May 11, 2006, in Atlanta, Georgia. The FR notice explains the purpose of the Workshop as follows:

> "The primary goal of the workshop is to bring together scientific and public health experts to develop a draft research agenda...to better understand the virulence, pathogenesis, host factors, and nonantimicrobial risk factors contributing to reports of morbidity and mortality associated with *Clostridium sordellii (C. sordellii) and Clostridium difficile (C. difficile)*. Additionally, our goals are to identify research needs and priorities that will enable rapid progress as well as to develop and provide recommendations for detecting cases and conducting surveillance of diseases and organisms."

Details for interested parties to apply to attend and/or participate in the workshop are available in the FR notice. Registrations must be received by April 15, 2006. Please be assured that, as always, the Agency remains committed to sharing emerging drug information with the public.

Your letter refers to a 1992 article by Lazar and others that studied the effect of RU-486's antiglucocorticoid properties on the development of septic shock in mice. We cannot say with certainly that this article was reviewed by the medical reviewer for the mifepristone new drug application (NDA), as it was not specifically referenced in the reviews. However, the article was included in the NDA for mifepristone, and medical officers review the entire NDA file in the course of conducting their reviews. With regard to your follow-up questions concerning the Lazar article, the Agency did not ask the drug's sponsor to conduct studies looking at IL-10 production in normal non-pregnant human females receiving mifepristone. Additionally, the available human data did not suggest a need to require further animal testing with regard to the role of mifepristone in sepsis. When the application was submitted in March of 1996 there had been over ten years of human experience with the drug product and it already had been approved for medical abortion in other countries.

Your letter inquires about the use by physicians of the FDA-approved Patient Agreement form. As part of the approval of Mifeprex, the sponsor, Danco Laboratories, is responsible for supplying the physician with the approved labeling, Medication Guide, and Patient Agreement when shipping the drug product to a physician. FDA is aware that physicians may choose to not use the materials that the sponsor supplies, and that some may have chosen to use a modified version of the Patient Agreement form. However, these decisions are made by physicians exercising their own judgment about what is best for their patients.

Further, FDA does not audit patient agreement forms. Those forms are kept by the physician and in the patient records, which FDA does not routinely have access to or examine. FDA has authority to and does audit the sponsor of Mifeprex, Danco Laboratories, to ensure that they are distributing the approved labeling, Medication Guide and Patient Agreement. FDA also audits the sponsor's records for the Physician Agreements.

Thank you for your interest in this important issue. If we can be of further assistance, please let us know.

Sincerely,

Patrick Ronan

Patrick Ronan
Associate Commissioner
for Legislation

Enclosures